Amendments to the Claims

Please amend Claims 44, 45, and 46 as shown below. This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

1. (Previously Cancelled) An antibody which catalyzes hydrolysis of β-amyloid at a predetermined amide linkage.

2. (Previously Cancelled) The antibody of Claim 1 which catalyzes hydrolysis of the amide linkage between residues 39 and 40 of β-amyloid.

3. (Previously Cancelled) The antibody of Claim 1 which catalyzes hydrolysis of the amide linkage between residues 40 and 41 of β-amyloid.

4. (Previously Cancelled) The antibody of Claim 1 which catalyzes hydrolysis of the amide linkage between residues 41 and 42 of β-amyloid.

5. (Previously Cancelled) The antibody of Claim 1 which preferentially binds a transition state analog which mimics the transition state adopted by β-amyloid during hydrolysis at a predetermined amide linkage, and also binds to natural β-amyloid with sufficient affinity to detect using an ELISA.

6. (Previously Cancelled) The antibody of Claim 1 which preferentially binds a transition state analog which mimics the transition state adopted by β-amyloid during hydrolysis at a predetermined amide linkage, and does not bind natural β-amyloid with sufficient affinity to detect using an ELISA.

7. (Previously Cancelled) A vectorized antibody which is characterized by the ability to cross the blood brain barrier and the ability to catalyze the hydrolysis of β-amyloid at a predetermined amide linkage.

8. (Previously Cancelled) The vectorized antibody of Claim 7 which is a bispecific antibody.

9. (Previously Cancelled) The vectorized antibody of Claim 8 which has a first specificity for the transferrin receptor and a second specificity for a transition state adopted by β-amyloid during hydrolysis.

10. (Previously Cancelled) The vectorized antibody of Claim 9 which catalyzes hydrolysis of β-amyloid between residues 39 and 40.

11. (Previously Cancelled) A method for sequestering free β-amyloid in the bloodstream of an animal, comprising the steps:
    a) providing antibodies specific for β-amyloid; and
    b) intravenously administering the antibodies to the animal in an amount sufficient to increase retention of β-amyloid in the circulation.

12. (Previously Cancelled) A method for sequestering free β-amyloid in the bloodstream of an animal, comprising the steps:
    a) providing an antigen comprised of an epitope which is present on endogenous β-amyloid; and
    b) immunizing the animal with the antigen of step a) under conditions appropriate for the generation of antibodies which bind endogenous β-amyloid.

13. (Previously Cancelled) A method for reducing levels of β-amyloid in the brain of an animal, comprising the steps:
    a) providing antibodies specific for β-amyloid endogenous to the animal; and
    b) intravenously administering the antibodies to the animal in an amount sufficient to increase retention of β-amyloid in the circulation of the animal.

14. (Previously Cancelled) The method of Claim 13 wherein the antibodies specific for β-amyloid are catalytic antibodies which catalyze hydrolysis of β-amyloid at a predetermined amide linkage.

15. (Previously Cancelled) The method of Claim 13 wherein the antibodies are monoclonal.

16. (Previously Cancelled) The method of Claim 13 wherein the antibodies are polyclonal.

17. (Previously Cancelled) The method of Claim 13 wherein the antibodies specifically recognize epitopes on the C-terminus of β-amyloid$_{1-43}$.

18. (Previously Cancelled) A method for reducing levels of β-amyloid in the brain of an animal, comprising the steps:
    a) providing an antigen comprised of an epitope which is present on β-amyloid endogenous to the animal; and
    b) immunizing the animal with the antigen of step a) under conditions appropriate for the generation of antibodies which bind endogenous β-amyloid.

19. (Previously Cancelled) The method of Claim 18 wherein the antigen is a transition state analog which mimics the transition state adopted by β-amyloid during hydrolysis at a predetermined amide linkage.

20. (Previously Cancelled) The method of Claim 18 wherein the antigen is comprised of $A\beta_{10-25}$.

21. (Previously Cancelled) The method of Claim 19 wherein the antibodies generated have a higher affinity for the transition state analog than for natural β-amyloid.

22. (Previously Cancelled) The method of Claim 19 wherein the antibodies generated catalyze hydrolysis of endogenous β-amyloid.

23. (Previously Cancelled) A method for preventing the formation of amyloid plaques in the brain of an animal, comprising the steps:
    a) providing an antigen comprised of an epitope which is present on β-amyloid endogenous to the animal; and
    b) immunizing the animal with the antigen of step a) under conditions appropriate for the generation of antibodies which bind endogenous β-amyloid.

24. (Previously Cancelled) The method of Claim 23 wherein the antigen is a transition state analog which mimics the transition state adopted by β-amyloid during hydrolysis at a predetermined amide linkage.

25. (Previously Cancelled) A method for reducing levels of circulating β-amyloid in an animal, comprising the steps:
    a) providing an antigen comprised of an epitope which is a mimic of a predetermined hydrolysis transition state of a β-amyloid polypeptide endogenous to the animal; and
    b) immunizing the animal with the antigen of step a) under conditions appropriate for the generation of antibodies to the β-amyloid hydrolysis transition state.

26. (Previously Cancelled) A method for reducing levels of circulating β-amyloid in an animal, comprising the steps:
    a) providing antibodies which catalyze the hydrolysis of β-amyloid endogenous to the animal; and
    b) intravenously administering the antibodies to the animal.

27. (Previously Cancelled) A method for preventing the formation of amyloid plaques in the brain of an animal, comprising the steps:
    a) providing antibodies which catalyze hydrolysis of β-amyloid produced by the animal at a predetermined amide linkage; and
    b) administering the antibodies to the animal in an amount sufficient to cause a significant reduction in β-amyloid levels in the blood of the animal.

28. (Previously Cancelled) A method for reducing levels of β-amyloid in the brain of an animal, comprising the steps:
    a) providing vectorized bispecific antibodies competent to transcytose across the blood brain barrier, which catalyze hydrolysis of β-amyloid of the animal at a predetermined amide linkage; and
    b) intravenously administering the antibodies to the animal.

29. (Previously Cancelled) The method of Claim 28 wherein the vectorized bispecific antibodies specifically bind the transferrin receptor.

30. (Previously Cancelled) The method of Claim 28 wherein the vectorized bispecific antibodies catalyze hydrolysis of the amide linkage between residues 39 and 40 of β-amyloid.

31. (Previously Cancelled) A method for disaggregating amyloid plaques present in the brain of an animal comprising the steps:

a) providing vectorized bispecific antibodies competent to transcytose across the blood brain barrier, which catalyze hydrolysis of β-amyloid produced by the animal at a predetermined amide linkage; and

b) intravenously administering the antibodies to the animal in an amount sufficient to cause significant reduction in β-amyloid levels in the brain of the animal.

32. (Previously Cancelled) A method for disaggregating amyloid plaques present in the brain of an animal, comprising the steps:

a) providing antibodies which catalyze hydrolysis of β-amyloid produced by the animal at a predetermined amide linkage; and

b) administering the antibodies to the animal.

33. (Previously Cancelled) A method for generating antibodies which catalyze hydrolysis of a protein or polypeptide comprising the steps:

a) providing an antigen, the antigen being comprised of an epitope which has a statine analog which mimics the conformation of a predetermined hydrolysis transition state of the polypeptide;

b) immunizing an animal with the antigen under conditions appropriate for the generation of antibodies to the hydrolysis transition state.

34. (Previously Cancelled) The method of Claim 33 wherein the protein is β-amyloid.

35. (Previously Cancelled) A method for generating antibodies which catalyze hydrolysis of a protein or polypeptide comprising the steps:

a) providing an antigen, the antigen being comprised of an epitope which has a reduced peptide bond analog which mimics the conformation of a predetermined hydrolysis transition state of the polypeptide;

b) immunizing an animal with the antigen under conditions appropriate for the generation of antibodies to the hydrolysis transition state.

36. (Previously Cancelled) The method of Claim 35 wherein the protein is β-amyloid.

37. (Previously Added) A bispecific antibody comprising:

a) a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier; and

b) a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope.

38. (Previously Added) The bispecific antibody of Claim 37 which is produced by fusing a first and a second hybridoma clone, the first hybridoma clone generating the specificity of step a) and the second hybridoma clone generating the specificity of step b).

39. (Previously Added) The bispecific antibody of Claim 37 which is produced by recombinant DNA techniques.

40. (Previously Added) The bispecific antibody of Claim 37 wherein the first and second antibody binding specificities are provided by chemically linking a first antibody, or fragment thereof, to a second antibody, or fragment thereof.

41. (Previously Added) The bispecific antibody of Claim 40 wherein the first and second antibodies are monoclonal antibodies.

42. (Previously Added) The bispecific antibody of Claim 40 which is an $F(ab')_2$ hybrid.

43. (Previously Added) The bispecific antibody of Claim 39 which is a single chain Fv heterobispecific dimer.

44. (Currently Amended) The bispecific antibody of Claim 37 wherein the second antibody specificity further confers the ability of the bispecific antibody to inhibit the formation of β–amyloid aggregates and plaques.

45. (Currently Amended) The bispecific antibody of Claim 37 wherein the second antibody binding specificity further confers the ability of the bispecific antibody to disaggregate preformed β–amyloid aggregates and plaques.

46. (Currently Amended) The bispecific antibody of Claim 37 wherein the second antibody specificity stabilizes β–amyloid in a transition state conformation and is further characterized by the ability to hydrolytically cleave β–amyloid.

47. (Previously Added) A method for inhibiting the formation of β-amyloid plaques in the brain of a human, the method comprising:

a) providing a bispecific antibody comprising:

i) a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier; and

ii) a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope; and

b) introducing the bispecific antibody of step a) into the circulatory system of the human at a concentration sufficient to result in transcytosis of the bispecific antibody across the blood brain barrier.

48. (Previously Added) The method of Claim 47 wherein the bispecific antibody is produced by fusing a first and a second hybridoma clone, the first hybridoma clone generating the specificity of step a) i) and the second hybridoma clone generating the specificity of step a) ii).

49. (Previously Added) The method of Claim 47 wherein the bispecific antibody is produced by recombinant DNA techniques.

50. (Previously Added) The method of Claim 47 wherein the first and second antibody binding specificities are provided by chemically linking a first antibody, or fragment thereof, to a second antibody, or fragment thereof.

51. (Previously Added) The method of Claim 50 wherein the first and second antibodies are monoclonal antibodies.

52. (Previously Added) The method of Claim 50 wherein the bispecific antibody is an $F(ab')_2$ hybrid.

53. (Previously Added) The method of Claim 49 wherein the bispecific antibody is a single chain Fv heterobispecific dimer.

54. (Previously Added) A method promoting the disaggregation of a preformed β-amyloid plaque in the brain of a human, the method comprising:

a) providing a bispecific antibody comprising:

i) a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier; and

ii) a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope in a preformed β-amyloid plaque thereby promoting the disaggregation of the plaque; and

b) introducing the bispecific antibody of step a) into the circulatory system of the human at a concentration sufficient to result in transcytosis of the bispecific antibody across the blood brain barrier.

55. (Previously Added) The method of Claim 54 wherein the bispecific antibody is produced by fusing a first and a second hybridoma clone, the first hybridoma clone generating the specificity of step a) i) and the second hybridoma clone generating the specificity of step a) ii).

56. (Previously Added) The method of Claim 54 wherein the bispecific antibody is produced by recombinant DNA techniques.

57. (Previously Added) The method of Claim 54 wherein the first and second antibody binding specificities are provided by chemically linking a first antibody, or fragment thereof, to a second antibody, or fragment thereof.

58. (Previously Added) The method of Claim 57 wherein the first and second antibodies are monoclonal antibodies.

59. (Previously Added) The method of Claim 57 wherein the bispecific antibody is an $F(ab')_2$ hybrid.

60. (Previously Added) The method of Claim 56 wherein the bispecific antibody is a single chain Fv heterobispecific dimer.

61. (Previously Added) A method inhibiting the formation of β-amyloid plaques in the brain of a human, the method comprising:

a) providing a bispecific antibody comprising:

i) a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier; and

ii) a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope, the second antibody further conferring the ability to catalyze the cleavage of β-amyloid, thereby inhibiting the formation of β-amyloid plaques by reducing levels of free β-amyloid available for incorporation; and

b) introducing the bispecific antibody of step a) into the circulatory system of the human at a concentration sufficient to result in transcytosis of the bispecific antibody across the blood brain barrier.

62. (Previously Added) The method of Claim 61 wherein the bispecific antibody is produced by fusing a first and a second hybridoma clone, the first hybridoma clone generating the specificity of step a) i) and the second hybridoma clone generating the specificity of step a) ii).

63. (Previously Added) The method of Claim 61 wherein the bispecific antibody is produced by recombinant DNA techniques.

64. (Previously Added) The method of Claim 61 wherein the first and second antibody binding specificities are provided by chemically linking a first antibody, or fragment thereof, to a second antibody, or fragment thereof.

65. (Previously Added) The method of Claim 64 wherein the first and second antibodies are monoclonal antibodies.

66. (Previously Added) The method of Claim 64 wherein the bispecific antibody is an $F(ab')_2$ hybrid.

67. (Previously Added) The method of Claim 63 wherein the bispecific antibody is a single chain Fv heterobispecific dimer.

68. (Previously Added) A therapeutic antibody that specifically binds an epitope contained within positions 10-25 of Aβ.

69. (Previously Added) A therapeutic antibody that sequesters Aβ peptide from its bound, circulating form in blood, and alters clearance of soluble and bound forms of Aβ in central nervous system and plasma.

70. (Previously Added) A therapeutic antibody that sequesters free β-amyloid in the blood and impedes passage of soluble β-amyloid out of the peripheral circulation.

71. (Previously Added) A therapeutic antibody that sequesters free β-amyloid in the blood, reduces levels of β–amyloid in the brain of an animal and prevents formation of amyloid plaques in the brain of the animal.

72. (Previously Added) The therapeutic antibody of claims 68-71 that is a whole antibody.

73. (Previously Added) The therapeutic antibody of claims 68-71 that is a fragment.

74. (Previously Added) The therapeutic antibody of claims 68-71 that specifically binds to an epitope having an amino acid between positions 10 and 25 of Aβ.

75. (Previously Added) The therapeutic antibody of claim 68-71 that specifically binds to an epitope having an amino acid between positions 14 and 25 of Aβ.

76. (Previously Added) The therapeutic antibody of claim 68, which specifically binds an epitope contained in positions 14-25 of said Aβ peptide.

77. (Previously Added) The therapeutic antibody of claims 68-71, which is a single chain antibody.

78. (Previously Added) An antibody fragment obtained from the therapeutic antibody of any one of claims 68-77.

79. (Previously Added) The fragment of claim 78, which is a Fab or F(ab')2 fragment.

80. (Previously Added) The fragment of claim 79, which is an F(ab')2 fragment.

81. (Previously Added) The fragment of claim 79, which is an Fab fragment.

82. (Previously Added) The therapeutic antibody or fragment of any one of claims 68-77, wherein the antibody or fragment thereof is produced in a myeloma cell.

83. (Previously Added) The therapeutic antibody or fragment of any one of claims 68-82, which, when administered peripherally to a human subject, does not need to cross the subject's blood-brain barrier to exert its beneficial effects.

84. (Previously Added) The therapeutic antibody or fragment of any one of claims 68-82, which, when administered peripherally to a human subject, does not require cellular responses in the subject's brain to exert its beneficial effects.

85. (Previously Added) The therapeutic antibody or fragment of any one of claims 68-82, which, when administered peripherally to a human subject, does not substantially bind aggregated Aβ in the subject's brain.

86. (Previously Added) The therapeutic antibody or fragment of any one of claims 68-82, which, when administered peripherally to a human subject, exhibits beneficial effects without necessarily binding to Aβ plaques in the brain.

87. (Previously Added) A nucleic acid, comprising a sequence coding for the light chain or the heavy chain of the antibody of any one of claims 68-86, or a fragment thereof.

88. (Previously Added) One or more nucleic acids, which when expressed in a suitable host cell, yield an antibody of any one of claims 68-86.

89. (Previously Added) An expression vector for expressing the antibody or fragment of any one of claims 68-86 comprising nucleotide sequences encoding said antibody or fragment.

90. (Previously Added) A cell transfected with the expression vector of claim 89.

91. (Previously Added) A cell transfected with two expression vectors of claim 89, wherein a first vector comprises a nucleotide sequence encoding a light chain and a second vector comprises a nucleotide sequence encoding a heavy chain.

92. (Previously Added) A recombinant cell that produces the therapeutic antibody or fragment of any one of claims 68-82.

93. (Previously Added) The cell of any one of claims 90-92, wherein the cell is a myeloma cell.

94. (Previously Added) A composition that comprises the antibody or fragment of any one of claims 68-86, and a sterile diluent.

95. (Previously Added) A method to inhibit the formation of amyloid plaques or the effects of toxic soluble Aβ species in humans, which method comprises administering to a human subject in need of such inhibition an effective amount of a therapeutic antibody or

fragment thereof that specifically immunoreacts with an epitope contained in positions 10-25 of Aβ.

96. (Previously Added) A method to reduce amyloid plaques or the effects of toxic soluble Aβ species in humans, which method comprises administering to a human subject in need of such reduction an effective amount of a therapeutic antibody or fragment thereof which specifically immunoreacts with an epitope contained in positions 10-25 of Aβ.

97. (Previously Added) A method to inhibit the formation of amyloid plaques or the effects of toxic soluble Aβ species in humans, which method comprises administering to a human subject in need of such inhibition an effective amount of a therapeutic antibody or fragment thereof that sequesters Aβ peptide from its bound, circulating form in blood.

98. (Previously Added) A method to reduce amyloid plaques or the effects of toxic soluble Aβ species in humans, which method comprises administering to a human subject in need of such reduction an effective amount of a therapeutic antibody or fragment thereof which sequesters Aβ peptide from its bound, circulating form in blood.

99. (Previously Added) The method of any of claims 95-98, wherein said antibody or fragment, when administered peripherally to humans, does not need to cross the blood-brain barrier to inhibit the formation of amyloid plaques or the effects of toxic soluble Aβ species.

100. (Previously Added) The method of any of claims 95-98, wherein said antibody or fragment, when administered peripherally to humans, does not require cellular responses to inhibit the formation of amyloid plaques or the effects of toxic soluble Aβ species.

101. (Previously Added) The method of any of claims 95-98, wherein said antibody or fragment, when administered peripherally to humans, does not substantially bind aggregated Aβ in the brain.

102. (Previously Added) The method of any one of claims 95-101, wherein the subject has or is at risk for Alzheimer's disease, or Down's syndrome.

103. (Previously Added) The method of any one of claims 95-101, wherein the subject is not diagnosed with Alzheimer's disease, or Down's syndrome.

104. (Previously Added) The method of any one of claims 95-103, wherein the antibody is administered by a peripheral route.

105. (Previously Added) The method of claim 104, wherein the antibody is administered by an intravenous route.

106. (Previously Added) A method of treating Alzheimer's disease, comprising administering to a patient in need thereof an effective amount of the antibody or fragment of any one of claims 68-86.